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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|-------------|-------------------------|---------------------|------------------|
| 09/932,483 | 08/17/2001 | Katalin Veronika Lukacs | 12071-010002 | 5360 |
| 22442 | 7590 | 08/01/2005 | EXAMINER | |
| SHERIDAN ROSS PC 1560 BROADWAY SUITE 1200 DENVER, CO 80202 | | | EWOLDT, GERALD R | |
| | | | ART UNIT | PAPER NUMBER |
| | | | 1644 | |

DATE MAILED: 08/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/932,483

Applicant(s)

LUKACS ET AL.

Examiner

G. R. Ewoldt, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 April 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2,4,6,7,14-31,33,39,40,53 and 54 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,2,4,6,7,14-31,33,39,40,53 and 54 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

1. Claims 1, 2, 4, 6, 7, 14-31, 33, 39, 40, 53, and newly added Claim 54, are pending and being acted upon.
2. Applicant's amendment and remarks, filed 4/27/05, are acknowledged. In view of said amendment the previous rejections under the second paragraph of 35 U.S.C. 112 and the first paragraph of 35 U.S.C. 112 (for the introduction of new matter) have been withdrawn.
3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
4. Claims 1, 2, 4, 6, 7, 14-31, 33, 39, 40, 53, and newly added Claim 54 stand/are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As set forth previously, A review of the art shows that little is known about the use of heat shock proteins for the treatment of eosinophilic inflammatory responses. There are some teachings that the administration of certain mycobacteria can be used to treat allergic responses, but the active component of the mycobacteria is not known. Accordingly, the specification must be looked to for guidance in the instant case. A review of the specification discloses that the method of the instant claims presumably treats Th2 mediated diseases by administering a heat shock protein to skew the immune response towards Th1. This method is, again presumably, based on the theory that there exists a Th1/Th2 balance wherein increasing the Th1 or Th2 response decreases the other. The experiments disclosed in the specification show that *M. leprae* HSP-65 can induce a T cell response and that administration of *M. leprae* HSP-65 before induction of airway hyperresponsiveness, in a mouse model, can abolish said hyperresponsiveness. Curiously, it is noted that whereas source and grade of other reagents such as ovalbumin is disclosed, the one reagent absolutely critical to the claimed method, the HSP, is merely disclosed as *M. leprae* HSP-65 in PBS, provided by Inventor Lukacs.

First note that many investigators consider the Th1/Th2 paradigm an overly simplistic way to view highly complex systems. See for example Louzoun et al. (2001) wherein the authors attempt to develop a mathematical model to account for contradictory results often seen in attempts to skew the Th1/Th2 ratio, e.g., enhancement (rather than the predicted suppression) of a Th1 mediated disease by the induction of a Th2 response. The authors conclude that Th1 and Th2 cells are more likely markers than effectors in certain diseases. Other authors have concluded that

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attempts to skew the Th1/Th2 ratio might be dangerous, see for example Brunet et al. (2002).

Even assuming the truth of the Th1/Th2 paradigm, the minimal disclosure of the specification is insufficient given the breadth of the claims. Note that many of the diseases specifically recited in the claims cannot be considered to be strictly Th2 mediated. See, for example, Shimada et al., which teaches that both Th1 and Th2 cytokines play a role in the development of atopic dermatitis. Clearly, simply increasing the Th1 response would not likely provide an effective treatment for this condition. Nance et al. teaches that the interstitial lung disease hypersensitivity pneumonitis is Th1 mediated. Again, increasing the Th1 response would not likely provide an effective treatment for this condition. Also see Mandic et al. which teaches that intrinsic asthma is also called nonallergic asthma (as opposed to extrinsic, allergic, asthma); it is unlikely that increasing the Th1 response would provide an effective treatment for this nonallergic (and non Th2 mediated) condition either.

Also note that not all heat shock proteins comprise the same immunological activities. Even the Inventor's own work, Rha et al. (2002), teaches that of 5 HSPs tested, only an unidentified *M. leprae* HSP had any immunological activity. It must also be noted that many investigators have found that the administration of HSPs can actually induce a Th2 response, see for example Francis et al. (2000).

Clearly then, the limited disclosure of the instant specification is insufficient support for the methods of the instant claims. In view of the quantity of experimentation necessary, the lack of sufficient working examples, the unpredictability of physiological activity, and the lack of sufficient specific guidance in the specification, it would take undue trials and errors to practice the claimed invention.

Applicant's arguments, filed 4/27/05, have been fully considered but they have not been found fully persuasive. Applicant has addressed the issue regarding whether or not certain diseases, e.g., atopic dermatitis, are Th1 or Th2 mediated by canceling the claims wherein specific diseases are recited. Applicant has addressed the issue regarding the oversimplicity of the Th1/Th2 paradigm by indicating that the issue is essentially irrelevant given the demonstration that the administration of *M. leprae* HSP-65 abolishes eosinophilic airway inflammation and hyperresponsiveness, induces a T cell response, upregulates IFN- γ , and downregulates IL-4 and IL-5 as claimed. Regarding the issue of safety, as set forth in Burnet et al., Applicant argues that the concern does not negate the utility of the claimed method to lessen the effects of certain cytokines on the inflammatory status of a tissue. Applicant cites the response to Burnet et al. by Wohlleben et al.

Regarding the issues addressed by Applicant, except the issues of Burnet et al., Applicant has overcome the rejection.

Two issues remain. First, looking to the complete response to Burnet et al. by Wohlleben et al., the authors state, "We

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agree totally with Rosa Brunet et al. that any vaccine that induces allergen-specific T helper 1 (Th1) responses has the potential for serious side-effects and therefore, cannot be used in humans at present. However, to date, this issue has not been resolved clearly and we feel that more research is needed before reaching the conclusion that the induction of allergen-specific Th1 responses should be discarded totally as a potential approach to anti-allergy vaccination." It is clear that in 2002, at least Burnet et al. and Wohlleben et al. were not of the opinion that the induction of a Th2 response *in vivo* was an acceptable treatment for allergy. While the idea might have potential, the idea did not rise to the level of invention.

One other issue also remains. As set forth previously, in all experiments disclosed in the specification, the therapeutic formulation, i.e., *M. leprae* HSP-65, was administered before the induction of disease, i.e., airway hyperresponsiveness or eosinophilia. Thus, there is no evidence of record that the method of the instant claims could be used to reduce an ongoing inflammatory response, i.e., a method that would be encompassed by the method of the instant claims.

5. No claim is allowed.

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

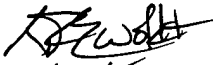
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina

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Chan can be reached on (571) 272-0841.

8. **Please Note:** Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


1/26/08
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